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10/035,349	10/19/2001	Luke V. Schneider	020444-000710US	2257

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EXAMINER

SISSON, BRADLEY L

ART UNIT PAPER NUMBER

1634

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

864

<b>Examiner-Initiated Interview Summary</b>	<b>Application No.</b> 10/035,349	<b>Applicant(s)</b> SCHNEIDER ET AL.	
	<b>Examiner</b> Bradley L. Sisson	<b>Art Unit</b> 1634	

**All Participants:**

**Status of Application:** 041

(1) Bradley L. Sisson.

(3) \_\_\_\_\_

(2) Kenneth E. Jenkins, Ph.D., Reg. No. 51,846.

(4) \_\_\_\_\_

**Date of Interview:** 2 September 2004

**Time:** 1:45 PM

**Type of Interview:**

- ☒ Telephonic  
☐ Video Conference  
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No

If Yes, provide a brief description:

**Part I.**

Rejection(s) discussed:

*See Continuation Sheet*

Claims discussed:

*1, 23, 26, and 48*

Prior art documents discussed:

*US Patent 6,194,144 B1 (Koster) issued 27 February 2001 and claiming benefit to 07 January 1993.*

**Part II.**

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:

*See Continuation Sheet*

**Part III.**

- ☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.  
☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

*Bradley L. Sisson*

(Examiner/SPE Signature)

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of rejections discussed: Possible rejection of claims under 35 USC 103(a) in light of teachings by US Patent 6,194,144 B1; Objection of claim 26; and rejection of claims under 35 USC 112, first paragraph, as it relates to language to "the proviso that said element is other than sulfur or phosphorus."

Continuation of Substance of Interview including description of the general nature of what was discussed: Mr. Sisson acknowledged receipt of the proposed amendment of 30 August 2004, and identified claim 23 as containing language similar in for directed to sulfur and phosphorus not being included. Dr. Jenkins indicated willingness to amend claim 23 so to correct this issue and to correct the dependency of claim 26.

Mr. Sisson expressed concern that a possible issue under 35 USC 103(a) may exist with regards to the disclosure of Koster, especially as found at columns 17-19, and given the definition of "mass defect label" as found at page 15, which reads in part: "The term 'mass defect' or 'mass defect label' refers to a portion of a label or the entire label that provides a mass sufficient and distinct to be readily identified in the mass spectrum of the sample... The most effective mass defect labels for use with typical organic chemicals (even chemicals containing group 1 and group 2 heteroatoms), such as biomolecules, incorporate one or more elements having an atomic number of 35 to 63. Examples of the most preferred mass defects are the elements bromine, iodine, europium and yttrium." Mr. Sisson noted that this definition differs from the art-accepted definition for "mass defect", which refers to the amount by which the mass of an atomic nucleus is less than the sum of the masses of its constituent particles. Dr. Jenkins agreed that applicant's definition did differ from that used in the art.

In response to inquiry by Mr. Sisson as to where mass defect is to be construed as being "less than 1 amu," Dr. Jenkins directed attention to page 21, second full paragraph, of the specification. Dr. Jenkins indicated that the clause directed the mass defect being less than 1 amu was added following discussions with the prior examiner. Dr. Jenkins indicated that he did not feel that this limitation added anything beyond what was an inherent aspect of the claimed method but was added to satisfy the concerns of the prior examiner. Mr. Sisson indicated agreement with this assessment.

While not discussed during the interview, Mr. Sisson notes that while the specification states that this effect is found for elements having atomic numbers 35 to 63, the claim recite that elements 17 to 77 are to be used. Accordingly, the aspect of this effect being found for the entire range (17 to 77) is not supported by the second full paragraph, of page 21 of the specification and as such, an issue of new matter may exist.

Mr. Sisson indicated that he considered applicant's "mass defect labels" to encompass at least some of the "mass modified" labels disclosed and used by Koster, noting with particularity that Koster teaches explicitly of using Chlorine (AN 17), Bromine (AN 35), and Iodine (AN 49); see column 18. Mr. Sisson directed attention to Koster, column 17, last two paragraphs, as teaching that by using their mass modified (mass defect) labels, they are able to sequence nucleic acids. Mr. Sisson noted that Koster does not teach using elements other than halogens which are included within applicant's recited range, and suggested that applicant consider narrowing the claims so to exclude halogens from the claims.

Dr. Jenkins asserted that Koster does not teach the claimed method, pointing to claim 1, step (d), that the "detection" requires a mass defect of less than one amu. Mr. Sisson noted that the claimed does not recite "detecting" a mass defect of less than one amu, or that any "detection" is performed, but rather, one is "determining the sequence of at least two terminal residues of said labeled oligomer" that a mass defect label of less than 1 amu. Mr. Sisson asserted that by using the same label so to sequence the same oligomer, by the same method (mass spectrometry), the label used in the method of Koster has as an inherent property, applicant's "mass defect [of] less than 1 amu" and that by sequencing the oligomer "at least in part" based upon the label (Koster, column 17), "unambiguous mass/sequence assignments are possible even in the worst case scenario" (Koster, column 19, penultimate paragraph). Mr. Sisson indicated that there may well be an issue under 35 USC 103(a) in this regard.

In response to inquiry by Mr. Sisson, Dr. Jenkins directed attention to page 58 as providing the usage of the term "root tag" as found in claim 48. While agreement was reached that support for the term exists in the file, agreement on the existence of a definition for same was not reached.

The parties agreed to hold a subsequent telephonic interview on October 6<sup>th</sup>.

**Sisson, Bradley**

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**From:** Jenkins, Kenneth E. [kejenkins@townsend.com]  
**Sent:** Monday, August 30, 2004 7:39 PM  
**To:** Sisson, Bradley  
**Subject:** Proposed Claims (10/035,349)

<<Proposed Mass Defect Clams.doc>>

Dear Examiner Sisson-

Thank you for your time and courteousness during our meeting today regarding U.S. Application Number 10/035,349 (the Mass Defect Application).

Per our discussion, enclosed please find proposed claim amendments for your review and possible Examiner's amendment. If you have any comments or questions, please don't hesitate to call me here in the San Diego office at (858) 350-6154.

I will be back in my home office on Wednesday where I can be reached at (415) 273-4787.

Please confirm receipt of this email.

Best regards.

Ken

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DRAFT

**PROPOSED CLAIM AMENDMENTS FOR EXAMINER'S REVIEW  
APPLICATION NUMBER 10/035,349**

1. (Currently Amended) A method for sequencing a terminal portion of an oligomer, comprising:

(a) contacting said oligomer with a mass defect labeling moiety to covalently attach the mass defect labeling moiety to a terminus of the oligomer and form a labeled oligomer, said mass defect labeling moiety comprising at least one element having an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus;~~

(b) fragmenting said labeled oligomer using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments;

(c) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and

(d) determining the sequence of at least two terminal residues of said labeled oligomer, wherein said sequence determination step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid.**

2. (Original) The method of claim 1, wherein said labeling moiety comprises at least one element of atomic number 35 to 63.

3. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element of atomic number 39 to 58.

4. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element selected from the group consisting of bromine, iodine, europium and yttrium.

5. (Original) The method of claim 4, wherein said element is europium.

6. (Original) The method of claim 4, wherein said element is yttrium.

7. (Original) The method of claim 4, wherein said element is bromine.

8. (Original) The method of claim 4, wherein said element is iodine.
9. (Currently Amended) The method of claim 1, wherein said oligomer is ~~selected from the group consisting of a protein, an oligonucleotide, an oligosaccharide and a lipid.~~
10. (Currently Amended) The method of claim ~~9~~ 1, wherein said oligomer is ~~an oligonucleotide~~ a polysaccharide.
11. (Original) The method of claim 9, wherein said sequence is at least three residues.
12. (Original) The method of claim 9, wherein said sequence is at least four residues.
13. (Original) The method of claim 1, wherein several oligomers, each labeled with a different number of mass defect elements are mixed prior to said fragmenting or analyzing step.
14. (Currently Amended) A method for sequencing a portion of an oligomer in an oligomer mixture, said method comprising:
- (a) contacting said oligomer mixture with a terminus labeling moiety to covalently attach the terminus labeling moiety to a terminus of said oligomer and form a labeled oligomer mixture, said terminus labeling moiety comprising at least one element having an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus;~~
  - (b) separating individual labeled oligomers in said labeled oligomer mixture; ~~and~~
  - (c) identifying a mass spectrum data corresponding to said individual labeled oligomer; and
  - (d) analyzing said mass spectrum data to determine the sequence of at least two terminus residues of said oligomer, wherein said analysis step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu.

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid.**

15. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 35 to 63.

16. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 39 to 58.

17. (Original) A method in accordance with claim 14, wherein said element is selected from the group consisting of bromine, iodine, europium and yttrium.

18. (Original) A method in accordance with claim 14, further comprising a step prior to step (a) of isolating a group of oligomers from a biological sample.

19. (Original) A method in accordance with claim 18, wherein said biological sample is from a diseased tissue sample.

20. (Original) A method in accordance with claim 18, wherein said biological sample is from a healthy tissue sample.

21. (Original) A method in accordance with claim 14, wherein said separating is conducted by at least one method of capillary electrophoresis of the labeled oligomer mixture.

22. (Original) A method in accordance with claim 14, wherein said mass spectrometric method uses ESI-TOF MS.

23. (Currently Amended) A method for structure and function analysis of an oligomer having a plurality of residues, said method comprising:

(a) contacting said oligomer with a mass defect labeling reagent to differentially label exposed residues and unexposed residues and produce a differentially labeled oligomer comprising a mass defect labeling moiety, wherein said mass defect labeling reagent comprises at least one element having an atomic number of from 17 to 77 that is other than sulfur or phosphorus;

(b) identifying a mass spectrum data corresponding to said differentially labeled oligomer; and

(c) analyzing said mass spectrum data to determine sequences of said oligomer that are exposed in the three-dimensional structure and sequences of said oligomer that are unexposed in the three-dimensional structure, wherein said analysis step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid.**

24. (Presently Amended) A method in accordance with claim 23, wherein said oligomer is a protein, ~~a nucleic acid, or an oligosaccharide.~~

25. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 35 to 63.

26. (Original) A method in accordance with claim 26, wherein said mass defect labeling reagent is bromine and said oligomer is a protein.

27. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 39 to 58.

28. (Original) A method in accordance with claim 23, wherein said differentially labeled oligomer is fragmented by enzymatic or chemolytic methods prior to step (b).

29. (Original) A method in accordance with claim 23, wherein said oligomer is a protein, said mass defect is bromine or iodine and said exposed residues comprises a portion of the tyrosine residues present in said protein.

30. (Original) A method in accordance with claim 23, wherein said mass spectrometric method uses ESI-TOF MS.

31. (Original) A method in accordance with claim 29, wherein said mass spectrometric method uses ESI-TOF MS.



32. (Currently Amended) A method for sequencing the terminal portion of an oligomer, comprising:

(a) contacting a first sample of said oligomer with a labeling moiety to covalently attach a label to the terminus of the oligomer and form a labeled oligomer, said labeling moiety having one element with an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus~~;

(b) contacting a second sample of said oligomer with a labeling moiety to covalently attach a label to a terminus of the oligomer and form a labeled oligomer, said labeling moiety having two elements with an atomic number from 17 to 77, ~~with the proviso that said elements are other than sulfur or phosphorus~~;

(c) optionally, repeating step (b) from one to three times with additional samples, wherein the labeling moieties have three, four or five elements, respectively, with an atomic number from 17 to 77, ~~with the proviso that said elements are other than sulfur or phosphorus~~;

(d) mixing the labeled oligomers from steps (a) through (c);

(e) fragmenting said labeled oligomers using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments;

(f) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and

(g) determining the sequence of at least two terminal residues of said labeled oligomer fragments, wherein said sequence determination step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid.**

33. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 35 to 63.

34. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 39 to 58.

35. (Original) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is a protein.

36. (Currently Amended) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is ~~an oligonucleotide~~ a nucleic acid.

37. (Currently Amended) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is ~~an oligosaccharide~~ a polysaccharide.

38. (Currently Amended) A method for sequencing a portion of an oligomer, comprising:

- (a) fragmenting aliquots of said oligomer using one or more specific enzymatic or chemolytic fragmentation methods to produce oligomer fragments, wherein a different fragmentation method is applied to each aliquot;
- (b) contacting a first aliquot of oligomer fragments with a first labeling moiety to covalently attach said first labeling moiety to a terminus of the oligomer fragments and form labeled oligomer fragments, said first labeling moiety having one element with an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus~~;
- (c) optionally contacting the other aliquots of oligomer fragments with other distinct labeling moieties to covalently attach said distinct labeling moieties to the termini of the oligomer fragments and form labeled oligomer fragments, said distinct labeling moiety having two or more elements with an atomic number from 17 to 77, ~~with the proviso that said elements are other than sulfur or phosphorus~~;
- (d) optionally mixing the aliquots of labeled oligomer fragments;
- (e) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and
- (f) determining the sequence of at least two residues of said labeled oligomer, wherein said sequence determining step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid.**

39. (Original) A method in accordance with claim 38, wherein said oligomer is a lipid.

40. (Original) A method in accordance with claim 38, wherein said oligomer is a protein.

41. (Original) A method in accordance with claim 38, wherein said oligomer is a nucleic acid.

42. (Currently Amended) A method in accordance with claim 38, wherein said oligomer is ~~an oligosaccharide~~ a polysaccharide.

43. (Original) A method in accordance with claim 38, wherein said elements have an atomic number of from 35 to 63.

44. (Original) A method in accordance with claim 43, wherein said elements have an atomic number of from 39 to 58.

45. (Currently Amended) A method for comparing the relative abundances of analytes from two or more samples, comprising:

(a) contacting the analytes of the first sample with a labeling moiety to covalently attach a label to the analytes and form labeled analytes, said labeling moiety having one element with an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus;~~

(b) contacting the analytes of subsequent samples with labeling moieties to covalently attach labels to the analytes in each sample, wherein the labeling moieties used for each subsequent sample contain an additional element with an atomic number from 17 to 77, ~~with the proviso that said elements are other than sulfur or phosphorus;~~

(c) mixing the aliquots of labeled analytes;

(d) identifying mass spectrum data corresponding to said labeled analytes; and

(e) analyzing said mass spectrum data to determine the relative abundances of one or more of the analytes between the samples, wherein said analysis step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu.

46. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 35 to 63.

47. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 39 to 58.

48. (Currently Amended) A method for tagging the elements of chemical libraries, either during synthesis or screening, comprising;

(a) contacting a root tag with a labeling moiety to covalently attach a label to the root tag and form a labeled tag, said labeling moiety having one element with an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus;~~

(b) optionally, contacting a root with additional labeling moieties to covalently attach additional labels to the root tag and form a multiply labeled tag, said labeling moiety having one element with an atomic number from 17 to 77, ~~with the proviso that said element is other than sulfur or phosphorus;~~

(c) identifying mass spectrum data corresponding to said labeled tag; and

(d) analyzing the mass spectrum data to determine both the mass and the number of elements with an atomic number from 17 to 77 of the labeled tag, such that the mass and number of elements identifies chemical processes to which a specific chemical of the library has been exposed and the identity of the chemical from the library, wherein said analysis step is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu.

49. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 35 to 63.

50. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 39 to 58.

**51.** (Previously Presented) The method of claim 1, wherein said sequence determination step comprises identifying a mass spectrum peak of a fragment comprising said labeling moiety based on the mass defect of said labeling moiety.

**52.** (Previously Presented) The method of claim 45, wherein at least a portion of said labeling moiety of step (a) is a stable isotope of said labeling moiety of step (b).

**53.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 2 or more but 16 or less stable isotopes.

**54.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 4 or more but 16 or less stable isotopes.

**55.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 8 or more but 16 or less stable isotopes.

**56.** (Previously Presented) The method of claim 52, wherein said stable isotope is selected from the group consisting of  $^2\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$  and  $^{81}\text{Br}$ .

**57.** (Previously Presented) The method of claim 45, further comprising separating at least a portion of said mixture of labeled analytes prior to said analysis step (d).

**58.** (Previously Presented) The method of claim 57, wherein said separation step comprises separating at least a portion of said mixture of labeled analytes by electrophoresis, chromatography or affinity separation.